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A new Hg^{2+} fluorescent sensors based on 1,3-alternate thiacalix[4]arene (L) and the complex of [L+Hg^{2+}] as turn-on sensor for cysteine

Fajun Miao, Junyan Zhan, Zhilong Zou, Deimei Tian, Haibing Li *

Key Laboratory of Pesticide and Chemical Biology (CCNU), Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, PR China

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ABSTRACT

A new thiacalix[4]arene derivative in a 1,3-alternate conformation bearing four naphthalene groups through crown-3 chains has been synthesized, which exhibits high selectivity toward Hg^{2+} by forming a 1:2 complex, among other metal ions (Na^{+}, K^{+}, Mg^{2+}, Ba^{2+}, Ca^{2+}, Sr^{2+}, Cs^{+}, Mn^{2+}, Fe^{2+}, Cd^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Li^{+}, and Zn^{2+}) with a low detection limit (3.30×10^{-7} M). The metal ion-binding properties were studied by fluorescence, AFM, and ^{1}H NMR spectroscopy. The in situ prepared [Hg^{2+}+L] complex shows well recognition ability for cysteine with a low detection limit (2.23×10^{-7} M) through fluorescence turning on. The mechanism of fluorescence turning on is the host L releasing from [L+Hg^{2+}] for [Cys+Hg^{2+}] complex formed. Thus the paper reports secondary-sensor design: Hg^{2+} as a first sensor for [L+Hg^{2+}] form, cysteine as a second sensor for Hg^{2+} releasing from the [L+Hg^{2+}] complex after cysteine adding in.

1. Introduction

The development of highly selective and sensitive fluorescent sensors, which are capable with dual monitoring of metal ions and amino acids, have attracted considerable attention because of their wide impacts on environment and biological monitoring.[1] Among the metal ions, Hg^{2+} is attracted much more attention because it could cause a variety of symptoms in vivo, including digestive, cardiac, kidney, and neurological diseases.[2] Generally, the damage of Hg^{2+} mainly takes place through the process of complex interactions between mercury and sulfur, which provided by amino acids and peptides in vivo.[3] In particular, Hg^{2+} ions are inactive toward other amino acids except cysteine in terms of the previous reports.[4] As one of the indispensable amino acids, cysteine plays vital and important roles in human body.[5] Therefore, detecting and sensing mercury and cysteine based on one fluorescent sensor with dual functionality is feasible, and which is more economical, convenient and also of great significance. There are several reports upon recognizing Hg^{2+} and cysteine individually. For the sake of Hg^{2+} detection, plenty of receptors have been applied, such as calix[4]crowns,[6] rhodamine,[7] calix[4]arene-diaza-crown ether,[8] and dipyrene-diamide.[9] Fluorescent sensors based on amino recognition also have been reported.[10] Therefore, detecting and sensing mercury and cysteine based on one fluorescent sensor with dual functionality is feasible, and which is more economic, convenient, and also of great significance. Keeping these in mind and encouraged by the recent brilliant achievements of competitive binding assays, such as Mirkin's.[11] As a result, a specific host for Hg^{2+} recognition and second detection of cysteine is quite demanded. Being famous for its excellent skeleton structure serving as molecular platform,[12] calixarene based on numerous derivative molecules have achieved wonderful recognization performances. Especially combined with the universal and popular 'click chemistry' technology, which endows the calixarene more recognization sites, such as triazole groups.[13] On the basis of the wonderful cooperative interactions between triazole and metal ions,[14] to achieve the Hg^{2+} recognization and secondary detection of cysteine by a clicked fluorescent calixarene is reasonable and meaningful. And to the best of knowledge, such a secondary sensor of cysteine recognization followed by Hg^{2+} detection has been no report.

Herein, we exploited a novel functionalized thiacalix[4]arene (L) by means of the classic 'click chemistry' methodology.[15] 1-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)naphthalene were chosen to graft onto the thiacalix[4]arene for the following two reasons: (i) thiacalix[4]arene considered as a desirable platform, the pre-formed triazole groups provided binding sites. (ii) The naphthalene groups offered fluorescent signals for the sensitive fluorescent detection. The prepared L was characterized by ^{1}H NMR, MS, elementary analysis. The verification performance of L toward recognition of metal ions is subsequently investigated. High selectivity and sensitivity upon Hg^{2+} was accomplished. Most significantly, the formed [Hg^{2+}+L] complex in the first step shows specific recognition of cysteine with high selectivity and sensitivity. The characteristic changes observed

* Corresponding author. Tel.: +86 27 67867958; e-mail address: lhbing@mail.ccnu.edu.cn (H. Li).

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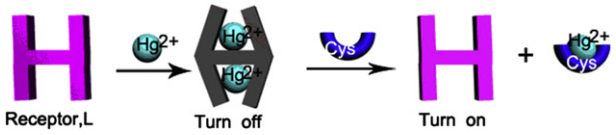
in the fluorescence spectroscopy during the sensing of Hg^{2+} as well cysteine are represented schematically in Scheme 1.



Scheme 1. Schematic representation of the primary and secondary sensing properties of L.

2. Results and discussion

2.1. Synthesis

The receptor molecule, L, has been synthesized as given in Fig. 1. All of these molecules including L were characterized satisfactorily by ^1H NMR, ^{13}C NMR, HRMS, and elemental analysis. The compound **1** with 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)naphthalene was carried out in DMF at 90 °C, with copper(II) sulfate and sodium ascorbate, to afford L (Fig. S4). A well-defined and simple ^1H NMR spectrum showed a highly symmetric structure for receptor L. The ^{t}Bu groups and aromatic protons of the thiacalix[4]arene moiety appeared as singlets at δ 1.08 ppm and δ 7.41 ppm, respectively. These δ values are in good agreement with the values obtained for 1,3-alternate conformers reported elsewhere.[16]

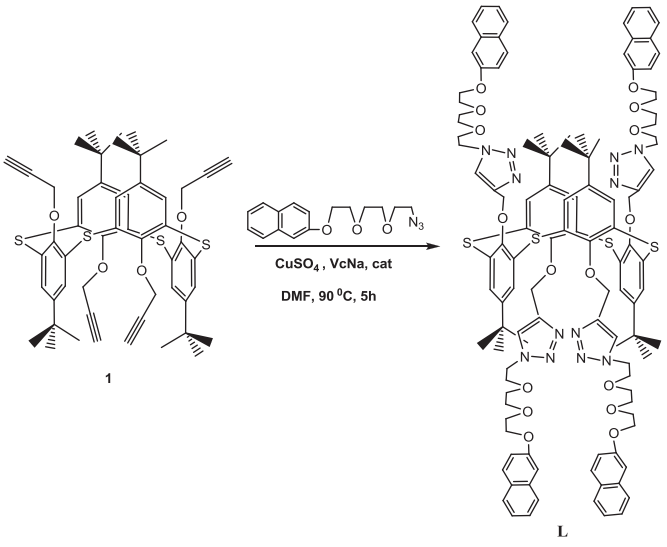


Fig. 1. Synthesis of the receptor L.

2.2. The properties of L in the selective recognition of Hg^{2+}

2.2.1. Fluorescence titration studies. The fluorescence spectrum of L (λ_{exc}=300 nm) in CH_3CN/H_2O (v/v, 3/1) exhibited a characteristic emission band at 354 nm. Upon addition of increasing amounts of Hg^{2+} to a solution of L in CH_3CN/H_2O (v/v, 3/1), quenching of fluorescence at 354 nm was observed instantaneously. Fluorescence titration of L (7×10^{-6} M) was conducted in CH_3CN/H_2O (v/v, 3/1) by the addition of Hg^{2+} from 0 to 2.1×10^{-5} M (Fig. 2). About 2 equiv of Hg^{2+} makes the quenched fluorescence reach a minimum. As the result, excess Hg^{2+} cannot achieve further quenching of fluorescence. Based on the mole ratio method, mole ratio between L and Hg^{2+} is 1:2, and meanwhile, the job's plots highly indicated a 1:2 mol ratio (Fig. S8). The detection of Hg^{2+} is about 3.3×10^{-7} M. Given the binding between the host and the guest, the binding constants could be calculated from the fluorescence

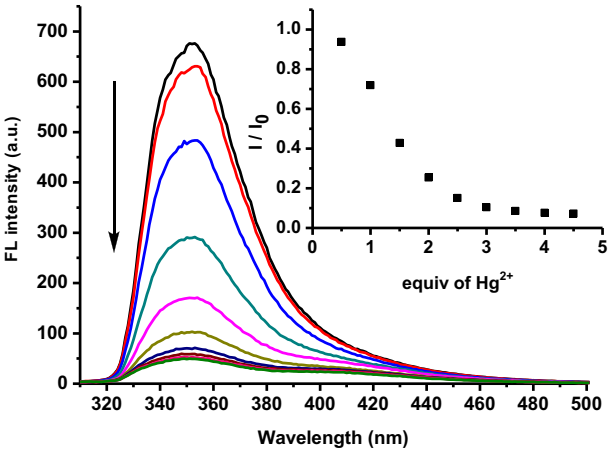


Fig. 2. Fluorescence spectra (λ_{exc}=300 nm) of L (7×10^{-6} M) in CH_3CN/H_2O (v/v, 3/1) with increasing amount of Hg^{2+} (0–3 equiv) in CH_3CN/H_2O (v/v, 3/1). Inset shows variation of fluorescence intensity against equivalents of Hg^{2+}. The excitation wavelength was 300 nm.

titration experiments. The titration curves were analyzed by the Hyperquad 2003 program[17] and the binding constants were calculated to be log K_{11}=8.75(2) and log K_{12}=14.23(4).

Under the above conditions, as shown in Fig. 3, the fluorescence of L (7×10^{-6} M) at 354 nm was strongly quenched by Hg^{2+}, no significant spectral changes occurred in the presence of 4 equiv each of Na^+, K^+, Mg^{2+}, Ba^{2+}, Ca^{2+}, Sr^{2+}, Cs^+, Mn^{2+}, Fe^{2+}, Cd^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Li^+, and Zn^{2+}. To find out whether L can detect Hg^{2+} selectively even in the presence of other metal ions, competitive metal ion titrations were carried out. Of practical significance is that even 14 equiv each of these metal ions did not interfere in the sensing of Hg^{2+}, and the results of the competition experiments are shown in Fig. 4. The origin of the fluorescence quenching may result from the electron or energy transfer from the excited naphthalene fluorescence to the Hg^{2+} ion. Alkali and alkaline earth metal ions showed no interaction with L, which may be due to their hard acid properties. Other transition and heavy metal ions produced insignificant fluorescence changes. Thus, while Hg^{2+} ion can be detected quantitatively in the presence of a number of biologically relevant Mn^+ ions.

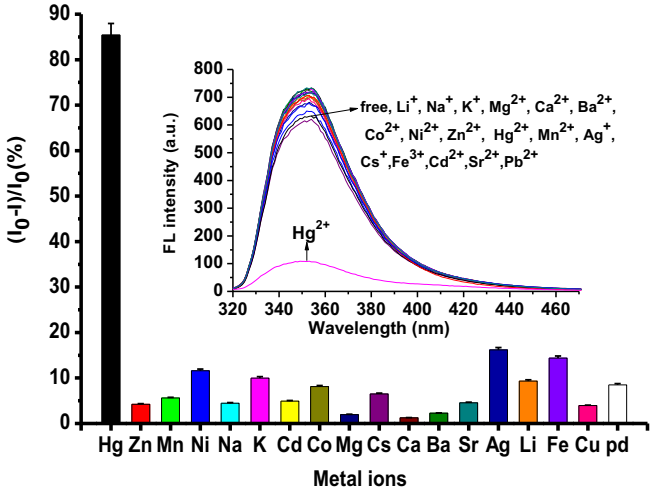


Fig. 3. Quench ratio $[(I_0-I)/I_0]$ of L (7×10^{-6} M) in CH_3CN/H_2O (v/v, 3/1) upon addition of 4 equiv of metal ions. The excitation wavelength was 300 nm. I_0 is the fluorescent emission intensity of the host at 354 nm, I is the fluorescent intensity after adding metal ions. Inset shows fluorescence intensity changes for L in CH_3CN/H_2O upon addition of metal ions.

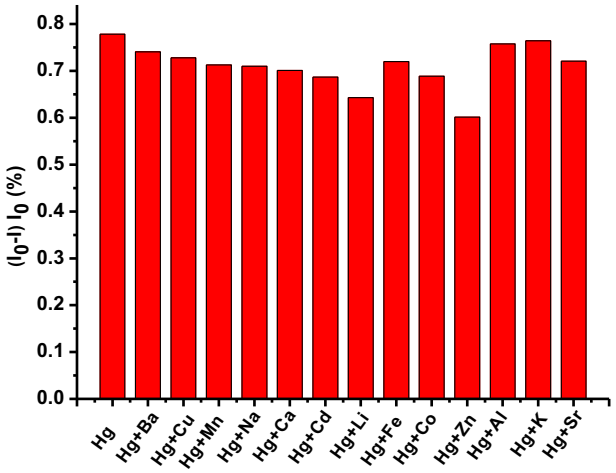


Fig. 4. Quench ratio $[(I_0-I)/I_0]$ of fluorescent intensity of L (7×10^{-6} M) in CH_3CN/H_2O (v/v, 3/1) upon the addition of 2 equiv of Hg^{2+} in the presence of 14 equiv of background metal ions. I_0 is the fluorescent emission intensity of the host at 354 nm, I is the fluorescent intensity after adding metal ions.

2.2.2. ^1H NMR study. To get first hand information about the coordinating sites of receptor L and Hg^{2+}, ^1H NMR of L (in DMSO-d_6) was carried out with $Hg(NO_3)_2$ (in DMSO-d_6) (Fig. 5). From the ^1H NMR spectra of L, upon the addition of $Hg(NO_3)_2$, absence of any changes observed in the chemical shift of aromatic and/or *tert*-butyl protons rules out any interaction between the arene of thiacalixarene and Hg^{2+}. If the Hg^{2+} were to be interacting with the arene cavity of the thiacalixarene, the protons would show corresponding shifts as reported in the literature by Shinkai and co-workers.[18] In the presence of 2.0 equiv of Hg^{2+}, the peak of the protons Ha on the triazole ring is shifted downfield by 0.216 ppm, whereas the OCH_2—triazole linker Hb is shifted downfield by 0.144 ppm. These ^1H NMR changes, especially the move of triazole proton Ha, suggest that the Hg^{2+} ion of the complex $[L+Hg^{2+}]$ may be located in the negative cavity formed by the nitrogen-rich triazole. These results are also fully in line with the fluorescence spectra changes (Fig. 2), which were observed for the complex $[L+Hg^{2+}]$.

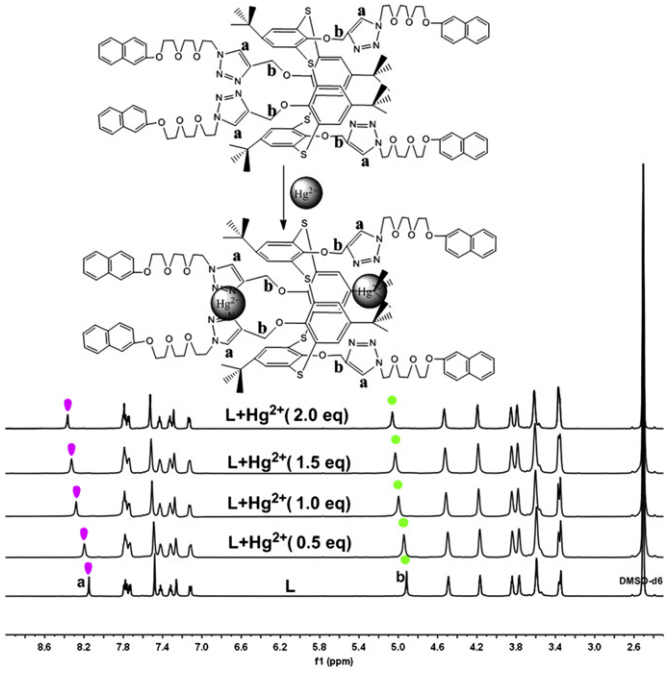


Fig. 5. NMR spectral changes of L by the addition of $Hg(NO_3)_2$ at 600 MHz in DMSO-d_6.

2.2.3. AFM studies. To determine whether the L reaction with Hg^{2+} is reflected in their nano structural features, AFM studies were performed with L, $[L+Hg^{2+}]$, and the corresponding micrographs and particle size distributions are shown in Fig. 6.

The micrographs show spherical particles in the case of L (Fig. 6a). The size particles are in the range of 312–396 nm, the height of these particles is in the range of 8.046–8.885 nm. The size present in these particles is similar to that observed in case of the aggregate of calix[4]arene as reported by recently.[19] When $Hg(NO_3)_2$ is added to L, the shape is changed to saclike, and the size of the particles is increased drastically to 323–690 nm (Fig. 6b). Most obvious, that the height of these particles is reduced drastically to 2.886–3.87 nm. Thus, both the size and shape of the particles differ between L and $[L+Hg^{2+}]$, suggesting that it is possible to identify the complex formation between L and Hg^{2+} by using nano structural features.

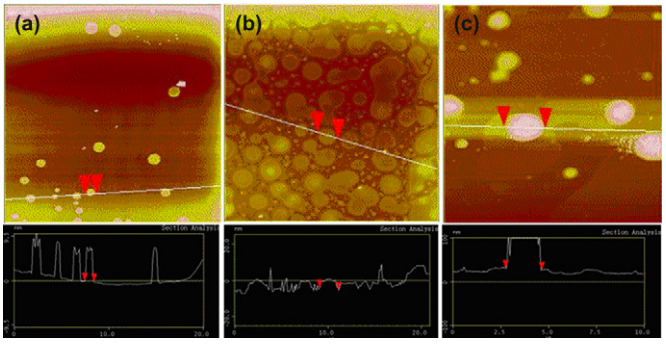


Fig. 6. AFM images of (a) L in CH_3CN/H_2O (v/v, 3/1). (b) $[L+Hg^{2+}]$ in CH_3CN/H_2O (v/v, 3/1). (c) $\{[L+Hg^{2+}]+Cys\}$ in CH_3CN/H_2O (v/v, 3/1).

2.3. Secondary sensor behavior of $[L+Hg^{2+}]$ and selective recognition of cysteine among naturally occurring amino acids

Since L recognizes Hg^{2+} clearly, the utility of $[L+Hg^{2+}]$ complex toward selective recognition of amino acid has been studied so that this complex can act as a secondary sensor.

2.3.1. Fluorescence titration. The chemosensing ensemble used in these titrations was prepared in situ by mixing L and Hg^{2+} in a 1:2 ratio. Out of 15 amino acids studied for their interaction, only Trp did not yield interpretable results owing to their strong emission that overlaps with the emission of L. The chemosensing mixture was titrated with all of the remaining naturally occurring 14 amino acids, where the fluorescence spectrum of $[L+Hg^{2+}]$ is altered only in the presence of cysteine (Fig. 7). After adding 5 equiv cysteine to the complex, the emission band at 354 nm was enhanced obviously. This is exactly reverse to what happens when L is titrated with Hg^{2+}, as reported in this paper, the Hg^{2+} is being removed from the complex by cysteine to release free L and thus the recognition of cysteine by $[L+Hg^{2+}]$ complex as a secondary sensor. The release of L in the titration of cysteine is followed by the formation of $[Cys+Hg^{2+}]$ complex, as it can form a stable complex with the thiol functionality.[1b,20] Under the above conditions, $[L+Hg^{2+}]$ has also been studied for its interaction with cysteine, which shows fluorescence recovery, as the concentration of cysteine increases. Fluorescence titration of $[L+Hg^{2+}]$ was conducted in CH_3CN/H_2O (v/v, 3/1) by the addition of cysteine from 0 to 1.2×10^{-5} M (Fig. 8).

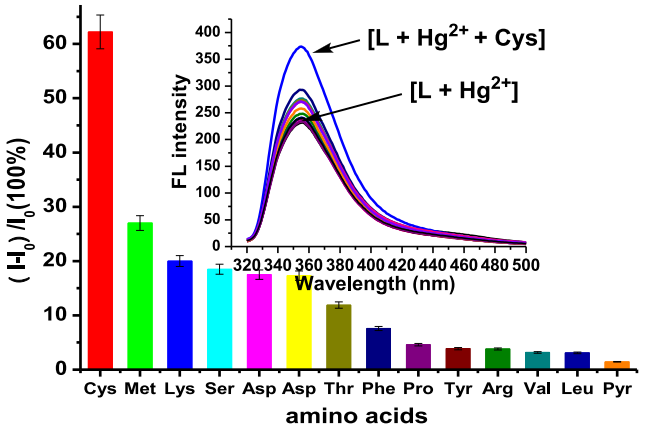


Fig. 7. Enhance ratio $[(I-I_0)/I_0]$ of fluorescent intensity of $[L+Hg^{2+}]$ upon addition of 5 equiv of amino acids. The excitation wavelength was 300 nm. I_0 is the fluorescent emission intensity of $[L+Hg^{2+}]$ at 354 nm, I is the fluorescent intensity after adding the 14 amino acids. Inset: fluorescence intensity changes for $[L+Hg^{2+}]$ in CH_3CN/H_2O (v/v, 3/1) upon addition of the 14 amino acids, 5 equiv.

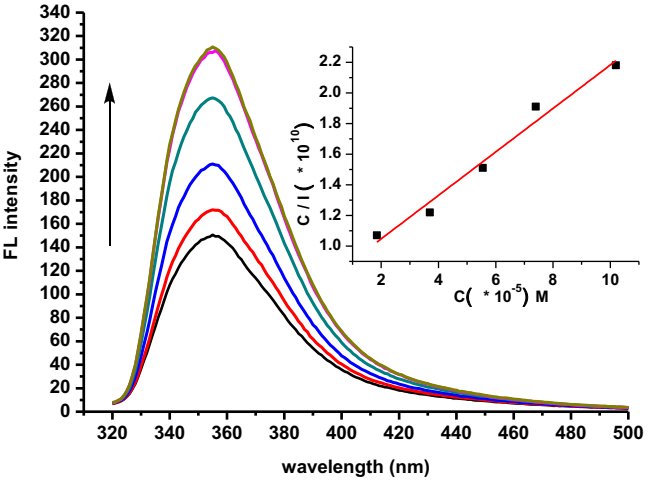


Fig. 8. Fluorescence spectra (λ_{exc}=300 nm) of $[L+Hg^{2+}]$ (5 μM) in CH_3CN/H_2O (v/v, 3/1) with increasing amount of cysteine (0, 1.85, 3.7, 5.5, 7.4, 10.2 μM, respectively) in CH_3CN/H_2O (v/v, 3/1). Inset: fluorescence intensity of $[L+Hg^{2+}]$ (5 μM) at 354 nm versus the concentration of cysteine added.

About 2 equiv of cysteine makes the quenched fluorescence reach restore to the largest. Excess cysteine cannot achieve further enhancing of fluorescence. It is found that cysteine increase the FL intensity of $[L+Hg^{2+}]$ in a concentration dependence (Fig. 8), that is, best described by a Langmuir-type equation.[21] A very high linearity (R^2=0.97133) is observed throughout the entire concentration range 1.85–10 μM of cysteine. The detection limit of cysteine is about 2.23×10^{-7} M.

2.3.2. ^1H NMR titration of $[L+Hg^{2+}]$ with cysteine and cysteamine hydrochloride. The release of L and the formation of the complex of Hg^{2+} have been further proven through ^1H NMR titration carried out between $[L+Hg^{2+}]$ and cysteine/cysteamine hydrochloride. The titration of $[L+Hg^{2+}]$ with cysteine could not be continued beyond 1 equiv owing to precipitation, therefore, the detailed titrations were carried out using cysteamine hydrochloride instead of cysteine, as the fluorescence behavior of both of these was found to be same. During the titration, the changes observed in the chemical shift can be seen in Fig. 9, as the concentration of cysteamine hydrochloride increases, the proton signals of $-OCH_2$, $-NCH$, are shifted and moved toward simple L. Thus it has been found that cysteamine hydrochloride removes Hg^{2+} from the binding core of calixarene using its $-SH$ function, resulting in the recovery of

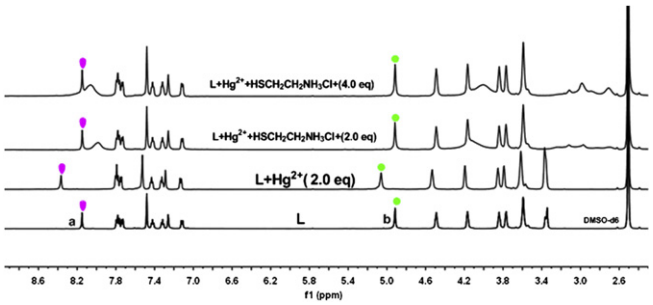


Fig. 9. The proposed structure of $[L+Hg^{2+}]$ for $HSCH_2CH_2NH_3Cl$, and increasing concentrations of $HSCH_2CH_2NH_3Cl$ in DMSO-d_6 at 298 K.

simple L from the $[L+Hg^{2+}]$. Since fluorescence changes occur only in the presence of cysteine and not with the other amino acids, the role of the $-SH$ function in Hg^{2+} binding was further confirmed by studying the ^1H NMR titration of $[L+Hg^{2+}]$ with cysteamine hydrochloride, because there only $-SH$ function in the cysteamine hydrochloride, the result of the ^1H NMR titration can provide powerful evidence for this.

2.3.3. AFM studies. To determine whether the release of L from the reaction of $[L+Hg^{2+}]$ with cysteine is reflected in their nano structural features, AFM studies were performed with {$[L+Hg^{2+}]$+Cys}, and the corresponding micrographs and particle size distributions are shown in Fig. 6c. Upon addition of cysteine to the complex, the saclike nano was completely disappeared, and there were appeared many white micron grade sphere. The micrographs are filled with particles arising from L and $[Hg^{2+}+Cys]$ complex. The white micron grade sphere may be the precipitation of $[Hg^{2+}+Cys]$, except for the micron grade sphere, all other spherical particles are in the range of 236–410 nm, these results are also fully in line with the range of L in the Fig. 6a. So these results also directly proved the release of L from reaction of $[L+Hg^{2+}]$ with cysteine.

3. Conclusion

In conclusion, we have synthesized a new 1,3-alternate derivative of thiacalix[4]arene L, which exhibited a highly selective toward Hg^{2+}. L is sensitive and selective toward Hg^{2+} over 15 other ions studied, viz., Na^+, K^+, Mg^{2+}, Ba^{2+}, Ca^{2+}, Sr^{2+}, Cs^+, Mn^{2+}, Fe^{2+}, Cd^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Li^+, and Zn^{2+}, as demonstrated by individual as well as competitive metal ion titrations. The complex formation between L and Hg^{2+} has been further followed by measuring ^1H NMR spectra as a function of added mercuric nitrate concentration. Comparison of the changes observed in the chemical shifts of different protons, suggests Hg^{2+} binding located in the negative cavity formed by the nitrogen-rich triazole in the thiacalixarene platform. The nano structural features of L and its complex of Hg^{2+} differ substantially to differentiate the complex from that of simple L. Most significantly, the $[L+Hg^{2+}]$ complex selectively recognizes cysteine among the naturally occurring amino acids to a lowest concentration of 2.23×10^{-7} M. The release of L has also been further proven on the basis of NMR titration. The present studies also demonstrate the necessity of the $-SH$ function in removing the Hg^{2+} from its complex of L based on NMR titration. That is, to say, L acts as a primary sensor toward Hg^{2+} and as a secondary sensor toward cysteine.

4. Experimental section

4.1. General remarks

All reactions were carried out in the oven-dried glassware. Every progress of the reactions was monitored by thin layer silicon,

purification was by column chromatography using silica gel (200–300 mesh). All chemicals used were of analytical reagent grade. NMR spectra were recorded at 600 (^{1}H) and 150 (^{13}C) MHz on a Bruker Avance DPX-300 FT NMR spectrometer. MALDI-TOF MS were obtained on a Bruker BIFLEXIII mass spectrometer. Fluorescence spectra were measured on a Hitachi F-4500 spectrometer. Metal ions as their salts were commercial and used without further treatment.

4.2. Synthesis

The receptor molecule, L, has been synthesized by three known steps starting from *p*-*tert*-butyl thiacalix[4]arene as given in Fig. 1, (see also Fig. S1). All of these molecules including L were characterized satisfactorily by ^{1}H NMR, ^{13}C NMR, and elemental analysis. The 1,3-alternate conformation of L has been confirmed by ^{1}H NMR spectroscopy.

4.3. Ligand L

Compound **2** (0.752 g, 2.5 mmol), calix[4]arene **1** (0.43 g, 0.5 mmol), $CuSO_4$ (0.5 g, 3.125 mmol), and sodium ascorbate (1.5 g, 7.5 mmol) were stirred in dry DMF (40 mL). The mixture was heated at 90 °C for 10 h, and then diluted with ethyl acetate (40 mL), and washed with water (3×30 mL). The organic phase was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, CH_3Cl/MeOH, v/v=20/1), yielding L as a white powder (440 mg, 75%). ^{1}H NMR (DMSO-d_6, δ ppm): δ 8.13 (s, 4H, CCH_2N), 7.78 (dd, J=11.2, 8.8 Hz, 8H, Na–H), 7.73 (d, J=8.1 Hz, 4H, Na–H), 7.47 (s, 8H, ArH), 7.42 (s, 4H, Na–H), 7.32 (d, J=7.6 Hz, 4H, Na–H), 7.26 (s, 4H, Na–H), 7.11 (dd, J=8.9, 2.4 Hz, 4H), 4.92 (s, 8H, OCH_2C), 4.49 (s, 8H, N–CH_2), 4.21–4.11 (m, 8H, OCH_2), 3.84 (d, J=5.1 Hz, 8H, OCH_2), 3.77 (d, J=4.2 Hz, 8H, OCH_2), 3.59 (d, J=3.6 Hz, 18H, OCH_2CH_2O), 0.96 (s, 36H, C(CH_3)). ^{13}C NMR ($CDCl_3$, δ ppm) δ 156.74 (s), 154.30 (s), 146.06 (s), 143.78 (s), 134.32 (s), 131.14 (s), 128.55 (s), 127.31 (s), 126.26 (s), 125.70 (s), 125.47 (s), 125.01 (s), 123.82 (s), 121.88 (s), 120.32 (s), 104.76 (s) (ArC, Na–C, CHN), 70.58 (d, OCH_2), 69.48 (d, OCH), 69.09–68.75 (m, OCH_2CH_2O), 67.67 (s, OCH), 64.03 (s, OCH), 49.78 (s, NCH), 33.96 (s, C(CH_3)$_3$), 31.00 (s,CH_3). EI(+) MS m/z=2078.89 ([M]$^+$ 100%). Anal. calcd for $C_{116}H_{134}N_{12}O_{16}S_4$: C, 66.96; H, 6.49; N, 8.08.

Acknowledgements

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.01.010.

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